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Effectiveness of non-pharmacological interventions in treating orthostatic hypotension in the elderly and people with a neurological condition

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Effectiveness of non-pharmacological interventions in treating orthostatic hypotension in the elderly and people with a neurological condition: a systematic review protocol

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Review question/objective: The objectives of the review are to determine:

- The effectiveness of non-pharmacological interventions for OH in elderly people and people with a neurological condition.
- Whether, in the elderly or people with a neurological condition who have OH, non-pharmacological interventions:
  - are effective in improving OH, resting blood pressure and cerebral blood flow
  - allow more or earlier mobilization (especially standing) to undertake activities of daily living and/or participate in rehabilitation programs

Specifically, the review question is:
What is the evidence base for non-pharmacological interventions in treating orthostatic hypotension (OH) in elderly people and people with a neurological condition?

Keywords Cerebral vascular accident; neurological condition; non-pharmacological; orthostatic hypotension; stroke

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Background

Orthostatic (postural) hypotension (OH) is defined by consensus as a sustained drop in systolic blood pressure of at least 20 mmHg and/or diastolic blood pressure of at least 10 mmHg within three minutes of moving from supine to standing or following head-up tilt to at least 60 degrees.[1,2]

In healthy individuals, a change in position from supine to upright results in approximately 500–1000 ml of blood moving from the upper body to the lower body, primarily the lower abdomen, buttocks and legs. This fluid shift produces a decrease in venous return, ventricular filling, cardiac output and blood pressure.[3] In healthy individuals, a compensatory reflex initiated by baroreceptors in the aortic arch and carotid sinus triggers tachycardia (increased heart rate) and vasoconstriction (narrowing of the blood vessels) that restores normal blood pressure in the upright position.[4] This compensatory mechanism is termed a baroreflex and is mediated by afferent and efferent autonomic peripheral nerves and is integrated within autonomic centers in the brainstem. Orthostatic hypotension is the result of baroreflex failure (autonomic failure), end-organ dysfunction or volume depletion.[5]

Orthostatic hypotension has both non-neurogenic and neurogenic causes and can be acute or chronic.[6] Non-neurogenic causes of OH fall into three categories: hypovolemia (reduced blood volume), cardiac pump failure and venous pooling. Hypovolemia can be caused by acute dehydration due to nausea and vomiting or to chronic blood loss from gastric ulcers. Cardiac pump failure can be caused by bradycardia, tachyarrhythmia, aortic stenosis or myocardial infarction. Venous pooling can be caused by prolonged standing motionless; however, it can also be caused by heat exposure, fever, severe varicose veins and postprandial dilation of splanchnic blood vessels. In addition, medications such as

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diuretics and anti-hypertensives can cause OH by interfering with autonomic reflex mechanisms and reducing intravascular volume.[5] Neurogenic OH is associated with neurological diseases and can be caused by abnormalities in either the central nervous system (e.g. stroke, spinal cord injury or Parkinson's disease) or peripheral nervous system (e.g. Guillain-Barré syndrome or diabetic neuropathy).[7]

Orthostatic hypotension can cause a variety of symptoms and is a frequent cause of syncope (transient loss of consciousness, rapid onset and short duration) that may contribute to morbidity, disability and even death, because of the potential risk of substantial injury.[1] Other characteristic symptoms of OH include: (a) dizziness/light headedness and pre-syncope; (b) weakness, fatigue and lethargy; (c) palpitations and sweating; (d) visual disturbances (including blurring, enhanced brightness and tunnel vision); (e) hearing disturbances (including impaired hearing, crackles and tinnitus); and (f) pain in the neck (occipital/para-cervical and shoulder region), low back pain or precordial pain.[8,9] These symptoms relate to the degree of the fall in blood pressure and hypoperfusion of the brain and other organs.

The prevalence of OH in elderly people (aged 50 years and over) is high, both in the United Kingdom (UK) and internationally, but variable depending on the characteristics of the population studied. Orthostatic hypotension is more common in elderly people who are hospitalized and institutionalized (up to 68%)[10] than in those living in the community (30%).[11] The high prevalence among hospitalized and institutionalized patients likely reflects multiple disease processes, including neurological and cardiac conditions, as well as the type and number of prescribed medications. In addition, orthostatic changes to blood pressure become more exaggerated after prolonged immobilization.[12] The prevalence of OH in people with neurological conditions is also high. Systematic reviews have concluded that OH occurs in approximately 40%[13] of people with Parkinson's disease and 50–82% of people with spinal cord injury, depending on the level of lesion.[14] Orthostatic hypotension is also very common in people with stroke and in a cohort of 71 people undergoing rehabilitation, 37 people (52.1%) had OH.[15] Given that stroke is predominately seen in elderly people, it is possible that the prevalence of OH post-stroke is much higher. This aligns with current European guidelines that highlight that OH is underdiagnosed.[1]

The presence of OH can interfere with and limit rehabilitation, especially in stroke where early mobilization (out-of-bed activities such as sitting, standing and walking) is undertaken at the earliest opportunity post-stroke.[16] Early mobilization is recommended by UK and European guidelines[17,18] and has demonstrated positive results in functional outcomes.[19] However, studies of early mobilization for people with acute stroke excluded people from the intervention arm if they had OH on three consecutive occasions.[18] Given the high incidence of OH in people with stroke, following this criterion in trials that involve standing as an early mobilization treatment intervention could limit the sample size and number of people potentially benefitting from this intervention. Furthermore, stroke is more common, although not exclusive, to people over 50 years of age,[20] and initial searching of the literature using MEDLINE, Embase, CINAHL, Cochrane Database and PROSPERO identified a paucity of evidence of interventions to treat OH in people with stroke. Therefore, a systematic review of people with neurological conditions and older people is required to provide healthcare professionals with evidence of the efficacy non-pharmacological interventions to treat OH. This may contribute positively toward the full participation of people with stroke in essential rehabilitation programs.

The goal of managing OH is to raise the patient's standing blood pressure without also raising their resting blood pressure, and specifically to reduce OH symptoms, increase the time they can stand and improve their ability to perform activities of daily living.[5] Currently, there is no specific intervention that achieves all of these goals, despite the multitude of pharmacological and non-pharmacological interventions available. A recent systematic review of pharmacological interventions highlighted that although there were multiple pharmacological interventions available in the UK, Europe and United States of America (USA), there were little high-quality data as to which was the best.[21] Furthermore, the review concluded that there are limited data on the benefits of long-term pharmacological interventions of OH in terms of the effects on postural blood pressure changes as well as symptom relief, suggesting that benefits should be weighed against potential side effects and adverse effects including cardiac failure, systolic hypertension and stroke.

Reviews[22] and guidelines[1,23] from the USA and Europe for the management of OH recommend non-pharmacological interventions as first line before progressing to pharmacological interventions if the former are ineffective or insufficient. A recent systematic review of non-pharmacological interventions to treat OH identified two general categories: physical modalities (exercise, functional electrical stimulation, compression [abdomen or lower limbs], physical counter-maneuvers, compression and sleeping with the head up) and dietary measures (food and fluid intake).[24] This review identified strong levels of evidence for several non-pharmacological interventions: compression of the legs and/or abdomen, physical maneuvers, functional electrical stimulation (for people with spinal cord injury) and size and timing of meals. This is aligned with a body of evidence identified in an initial review of the literature using MEDLINE, Embase, CINAHL, Cochrane Database and PROSPERO. However, people with neurological conditions often have complex needs and severe disability, which means that some non-pharmacological interventions may not be appropriate. For example, undertaking physical maneuvers requires a specific level of mobility and balance, and functional electrical simulation may be contraindicated due to other medical conditions or skin frailty. Therefore, the results of this review cannot be adequately transferred to people with neurological conditions, and this therefore underpins the rationale for the proposed review. There are a number of non-pharmacological interventions for OH that are used in the elderly and in people with other neurological disorders such as spinal cord injury and Parkinson's disease.[25,26] Interventions include the use of graduated compression garments with observational studies suggesting that abdominal supports are better at preventing OH compared to leg garments.[25] Compression garments allow repeated safe standing and/or sitting out, and with such training people can develop orthostatic tolerance. Orthostatic hypotension prevents mobilization at the time of occurrence, and this is problematic for people who are undergoing rehabilitation, for example, people with acute stroke. Non-pharmacological interventions such as compression garments are not commonly used early post-stroke, and a clear guidance on their use is lacking. Previous reviews of standing in people with neurological conditions[27] have highlighted the need to undertake a review of the effects of standing on OH and understanding the effectiveness of non-pharmacological interventions are a research priority for people with OH for older people and people with a neurological disease.[28]

An initial search of the literature – MEDLINE, Embase, CINAHL, Cochrane Database and PROSPERO – identified one systematic review from Canada examining studies that evaluated non-pharmacological interventions to treat OH.[24] However, this review was broad, covering various patient populations and not restricted to elderly people or people with a neurological condition. Furthermore, the review did not focus on any specific outcomes such as impact on mobilization or functional ability. Therefore, a systematic review of non-pharmacological interventions to treat OH in the elderly and people with a neurological condition is essential. This, coupled with a recent systematic review of pharmacological interventions,[21] will allow the development of a protocol to enable healthcare professionals to assess and treat OH in the early stages of people with acute stroke.

In conclusion, it is suggested that this proposed systematic review will provide novel information. It is specific to elderly people and people with a neurological condition and will include experimental and epidemiological studies.

Inclusion criteria

Types of participants

The current review will consider studies that include people diagnosed with OH by a doctor or other medical professional using criteria such as the International Classification of Diseases and Related Health Problems (ICD-10).[29] People aged 50 years and over will be included. Currently, there is no agreed definition of ''older'' or ''old people'' with ages differing widely as to what is considered ''old''. However, 50 years was accepted as the definition of older people for the purpose of the World Health Organization Older Adult Health and Ageing in Africa project[30] and will be used for the purposes of this review. In addition, people aged 18 years and over with a neurological condition of the central nervous system, both progressive, such as multiple sclerosis, Parkinson's disease, dementia, or sudden non-progressive, such as spinal cord injury and stroke. Peripheral nervous system conditions will be excluded.

Participants receiving treatment for acute or chronic OH will be included, which may encompass treatment being carried out in acute and community hospitals, outpatient clinics, in-patient rehabilitation units and the community (either in their own homes or in a residential or nursing home setting).

Types of intervention(s)

The current review will consider studies that evaluate non-pharmacological interventions to treat OH, which may include compression garments (e.g. lower limb compression stockings or abdominal corset); neuromuscular stimulation; physical maneuvers (e.g. squatting and bending at the waist) and isometric exercises for arms, lower limbs and abdominal muscles during standing; raising head of bed at nighttime; elimination of any offending agents (a-blockers and diuretics) or increasing fluid and salt intake. However, a full systematic search may identify additional interventions that will be considered. Interventions of any duration, frequency or intensity will be considered.

Comparator

The current review will consider studies that compare the non-pharmacological interventions listed above with no intervention, pharmacological interventions and/or other non-pharmacological interventions not listed above.

Outcomes

Outcomes will include systolic blood pressure, diastolic blood pressure (both lying and standing using manual or automated device) including time to symptoms and time to recovery; resting heart rate using manual or automatic device; cerebral blood flow using transcranial Doppler or correlation spectroscopy and others; observed and/or perceived symptoms; tolerance of therapy (e.g. ability to participate in therapy measured in length and frequency of sessions); duration of standing or sitting in minutes; and adverse events/effects where this information is provided.

Types of studies

Experimental and epidemiological study designs including randomized controlled trials, non-randomized controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies will be considered. Descriptive epidemiological study designs including case series, individual case reports and descriptive cross-sectional studies will also be considered.

Search strategy

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE, AMED, CINAHL and Embase will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the articles. A second search using all identified keywords and index terms will then be undertaken across all included databases. Third, the reference list of all identified reports and articles will be searched for additional studies. Studies published in English will be considered for inclusion in this review. The initial scoping search identified literature dated 1983; however, to ensure that the review has comprehensively captured all possible data with regard to the review question, there will be no lower date limit. The upper date limit will be present day of searching.

The databases to be searched include:
MEDLINE (Ovid)
Embase (Ovid)
The Cochrane Central Register of Controlled Trials
CINAHL
AMED (EBSCO)
PEDro

The search for unpublished studies will include scanning of references of identified studies, unpublished studies and gray literature. It will be undertaken using Google Scholar, Conference Papers Index and a search of clinical trials registers via www.controlled-trials.com and http://clinicaltrials.gov.

Initial keywords to be used will be ''stroke'' (MeSH) or ''post-stroke'' or ''poststroke'' or ''post stroke'' or ''CVA'' or ''cerebral vascular accident'' or ''cerebrovascular accident'' or ''cerebrovascular disease'' or ''cerebral vascular disease'' or ''upper motor neurone disorder'' or ''neurological'' or ''neuro'' or ''neurology'' or ''brain injury'' or ''hemorrhage'' or ''Parkinson's disease'' or ''multiple sclerosis'' or ''spinal cord injury''
''nonpharmacological'' or ''non pharmacological'' or ''non-pharmacological'' or ''non-invasive''

''pressure (active or passive)'' or ''bandages'' or ''splint'' or ''compression'' and ''abdominal'' and/or ''legs'' or ''lower limbs''
''orthostatic hypotension'' (MeSH) or ''postural hypotension'' or ''orthostasis'' or ''low blood pressure'' or ''vascular response'' or ''autonomic dysfunction''
''cerebral blood flow''
''function'' or ''functional outcome'' or ''activities of daily living''
''quality of life''

An example of the search strategy for MEDLINE (OVID) is included in Appendix I.

Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix II). Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer.

Data extraction

Data will be extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix III). These data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Authors of primary studies will be contacted for missing information or to clarify unclear data.

Data synthesis

Quantitative data will, where possible, be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard Chi-square, I^2 of 60% for moderate heterogeneity[31] and also explored using subgroup analyses based on the different study designs included in this review. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

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Appendix I: Search strategy example

1.	orthostatic adj2 hypotension [.ti; .tw; .mp]
2.	exp hypotension, orthostatic/ [MeSH] [.ti; .tw; .mp]
3.	postural adj2 hypotension [.ti; .tw; .mp]
4.	Orthostasis [.ti; .tw; .mp]
5.	dizziness/ [MeSH] [.ti; .tw; .mp]
6.	''low blood pressure'' [.ti; .tw; .mp]
7.	hypotension/ [MeSH] [.ti; .tw; .mp]
8.	vascular adj2 response [.ti; .tw; .mp]
9.	''autonomic dysfunction'' [.ti; .tw; .mp]
10.	''cerebral bloodflow'' or ''cerebral blood flow'' [.ti; .tw; .mp]
11.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12.	elderly or ''older people'' or ''older person*'' or aged/ or aging or ageing or senior* or geriatric [.ti; .tw; .mp]
13.	11 and 12
14.	''non-pharmacological treatment*'' or ''nonpharmacological treatment*'' or ''non pharmacological treatment*'' [.ti; .tw; .mp]
15.	''non-pharmacological management'' or ''nonpharmacological management'' or ''non pharmacological management [.ti; .tw; .mp]
16.	''non-pharmacological intervention*'' or ''nonpharmacological intervention*'' or ''non pharmacological intervention*'' [.ti; .tw; .mp]
17.	14 or 15 or 16
19.	13 and16
20.	11 and 17
20.	Compression adj2 garment* [.ti; .tw; .mp]
21.	Compression adj2 stocking* [.ti; .tw; .mp]
22.	Compression adj2 bandag* or compression therapy [.ti; .tw; .mp]
23.	Compression adj2 wrap [.ti; .tw; .mp]
24.	Stockings, compression/ [MeSH] [.ti; .tw; .mp]
25.	Abdominal adj2 binder [.ti; .tw; .mp]
26.	20 or 21 or 22 or 23 or 24 or 25
27.	11 and 26

28.	Rehabilitation [.ti; .tw; .mp]
29.	11 and 28
30.	''Functional electrical stimulation'' [.ti; .tw; .mp]
31.	11 and 30
32.	Exercise [.ti; .tw; .mp]
33.	11 and 32
34.	Physical manoeuvres [.ti; .tw; .mp]
35.	11 and 34
36.	Diet [.ti; .tw; .mp]
37.	Fluid [.ti; .tw; .mp]
38.	Meal* [.ti; .tw; .mp]
39.	Water [.ti; .tw; .mp]
40.	Food [.ti; .tw; .mp]
41.	36 or 37 or 38 or 39 or 40
42.	11 and 41
43.	parkinson* or alzheimer* or dementia or ''multiple sclerosis'' or ''motor neuron*'' or stroke [.ti; .tw; .mp]
44.	exp Stroke [MeSH] [.ti; .tw; .mp]
45.	exp ''Neurodegenerative diseases'' [MeSH] [.ti; .tw; .mp]
46.	exp Dementia [MeSH] [.ti; .tw; .mp]
47.	exp ''Multiple sclerosis'' [MeSH] [.ti; .tw; .mp]
48.	exp Cerebrovascular adj2 disease [MeSH] [.ti; .tw; .mp]
49.	exp ''Brain ischemia'' [MeSH] [.ti; .tw; .mp]
50.	exp ''Spinal cord injur*'' [MeSH] [.ti; .tw; .mp]
51.	exp Brain adj2 injur* [MeSH] [.ti; .tw; .mp]
52.	exp Craniocerebral adj2 trauma [MeSH] [.ti; .tw; .mp]
53.	exp ''Central nervous system diseases'' [MeSH] [.ti; .tw; .mp]
54.	exp Brain damage, chronic/ [MeSH] [.ti; .tw; .mp]
55.	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56.	11 and 55
56.	13 and 55
57.	11 and 17 and 55

Appendix II: Appraisal instruments

MAStARI appraisal instrument

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was study based on a random or pseudo-random sample?	☐	☐	☐	☐
2. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
3. Were confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
4. Were outcomes assessed using objective criteria?	☐	☐	☐	☐
5. If comparisons are being made, was there sufficient descriptions of the groups?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2. Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3. Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4. Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5. Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

_____

_____

_____

Appendix III: Data extraction instruments

MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting

Population

Sample size

Group A _____ Group B _____

Interventions

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

